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10/523,617	01/06/2006	Jillian Cornish	11752-010US1	1861

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EXAMINER	
BRADLEY, CHRISTINA	
ART UNIT	**PAPER NUMBER**
1654	

DATE MAILED: 06/27/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/523,617	CORNISH ET AL.	
	Examiner	Art Unit	
	Christina Bradley	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *02 June 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-38* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-38* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *02/01/05, 06/02/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicants elected SEQ ID NO: 3 without traverse. Claims 1-38 are pending.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 1-38 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

4. To provide evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of compete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof.

5. Claims 1-38 are drawn to preptin, preptin analogues and preptin agonists. The breadth of these claims is significant. The term preptin as defined in the specification encompasses all sequences of formula (I): 512 different peptide sequences. Analogs include functional equivalents of all 512 sequences of Formula (I). Functional equivalents include all proteins

which are immunologically cross-reactive with and have substantially the same function as preptin including fragments, active sites, substitutions, additions, deletions or fusions with other amino acids. A preptin agonist is a compound which has a high affinity for a preptin-binding receptor and promotes the proliferation of bone cells. A preptin agonist can be a peptide between 17 and 110 amino acids in length that contains any part of SEQ ID NOs: 1, 2 or 3. Sequences with at least 60% identity to SEQ ID NOs: 1, 2 and 3 are claimed.

6. The specification discloses the complete structure of the preptin analogues of Formula (I) however evidence that these peptides are effective at promoting bone cell growth is provided only for rat and human preptin (SEQ ID NOs: 2 and 3, respectively). The specification does not provide the complete or partial of a single additional species that meets the functional limitations of the claimed invention. With respect to agonists, which are described as those compounds exhibiting a tight binding affinity to the preptin receptor, the identity of the receptor is not known. Thus, it is not possible to measure the affinity of a potential agonist to determine if it meets the definition of agonist outlined in the specification. In addition, the specification fails to describe the physical and chemical properties that are essential for active forms of preptin and its analogues or agonists. Data is not presented in the specification or in the prior art that identifies the residues or chemical groups that give rise to receptor binding and activation. Likewise, the structural requirements for the claimed function are not disclosed. Finally, the application does not describe an assay for identifying additional active compounds or a means to predict which species would be effective. Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus.

7. *Vas-Cath Inc. v. Mahurkar*, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116).

8. With the exception of SEQ ID NOs: 2 and 3, the skilled artisan cannot envision the detailed chemical structure of preptin or its analogues and agonists that is capable of affecting bone cell growth. Therefore, conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

9. One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

10. Therefore, only the use of SEQ ID NOs: 2 and 3, but not the full breadth of the claims, meets the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

11. Claims 1-38 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the use of rat and human preptin (SEQ ID NOs:2 and 3, respectively), does not reasonably provide enablement for the use of all other preptins, preptin analogues or preptin agonists in the claimed methods or applications. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

12. The factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described in *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988). Among these factors are: (1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary. When the above factors are weighed, it is the examiner's position that one skilled in the art could not practice the invention without undue experimentation.

(1) the nature of the invention

13. The invention is drawn to methods for treating bone conditions, increasing and maintaining bone density and stimulating osteoblast growth by administering preptin, preptin analogues or preptin agonists.

(2) the state of the prior art

14. Preptin, a 34-amino acid peptide hormone that increases glucose-mediated insulin secretion, has been recently isolated from the same secretory vesicles that contain insulin and amylin from the pancreatic β-cells (Buchanan *et al.*, citation AQ in Information Disclosure Statement of 02/01/2006). However, its use in the treatment of bone conditions has not been previously reported.

(3) the relative skill of those in the art

15. The relative skill of those in the art is high.

(4) the predictability or unpredictability of the art

16. Experimental information on the structure and activity of each of the claimed species is not available either in the specification or the prior art. Thus, lacking experimental data, the skilled artisan is left to predict which preptin analogues or agonists would be effective in the claimed application. The ability to predict whether or not a particular analogue or agonist of preptin is active depends on the ability to predict the structure of the peptide, the ability to predict the interaction of the peptide and receptor, and the ability to predict whether or not a given interaction will succeed in activating the receptor.

17. Regarding structure prediction, the state of the art, though advanced in recent years, is not at a level to provide the detailed atomic- resolution information necessary to predict ligand-receptor interactions. In their recent review of the field Ginalski *et al.* (*Nuc. Ac. Res.*, **2005**, *33*, 1874) write: "Unfortunately, the protein structure prediction field is currently unsuccessful in keeping its promise of making the drug development process much more efficient. Predicted

protein structures can be used if very close homologs with known structure are available, but in most cases rational drug design requires iterative co-crystallization of the protein-ligand complexes. In the majority of cases, predicted models are of insufficient quality to offer atomic details necessary for lead optimization. Currently available structure prediction methods do not allow for high-quality predictions of the quaternary structure of protein complexes and for the prediction of interactions between proteins. Current benchmarks indicate that methods predicting interactions can be successful mainly in case when structures exhibit minimal conformational changes upon complex formation. Substantial errors observed n predicted models go beyond the limits tolerated by such methods."

18. Even when a protein structure is known and its activity well-established, it is difficult to predict the effect of individual amino acid substitutions or deletions. Rudinger (Peptide Hormones (Ed. J.A. Parson). University Park Press. Baltimore, 1976, pp. 1-7) states: "The significance of particular amino acids or sequences for different aspects of biological activity cannot be predicted a priori but must be determined from the case to case by painstaking experimental study." Recent examples in the art suggest that Rudinger's assessment of the unpredictability of amino acid substitution effects is still valid. Pitt *et al.* (*Nuc. Ac. Res.*, **2000**, *28*, 4419) report that random mutagenesis of the σ^{54} RNA polymerase uncovered five independent single amino acid substitutions that lead to defective transcription. Bradley *et al.* (*J. Mol. Biol.*, **2002**, *324*, 373) demonstrate that an Ala -> Gly substitution in six analogous structural environments of an ankyrin repeat protein have remarkably diverse effects on protein stability. Flanagan *et al.* (*Proc. Natl. Acad. Sci. USA*, **1992**, *89*, 748) show that the deletion of thirteen amino acids from the C-terminus of the 149-residue staphylococcal nuclease results in a

loss of 50% of the helicity but does not cause the protein to unfold into a disordered chain. A dramatic example of the effect of single amino acid substitutions is in sickle cell anemia. This disease, characterized by chronic haemolysis and susceptibility to infection, is caused by a single Glu -> Val substitution in the β-globin gene (Schnog *et al. J. Med.*, **2004**, *62*, 364). Finally, Sawai *et al.* (*Prot. Engin.*, **2002**, *15*, 225) show that this lack of predictability extends to short peptides as well: specific single amino acid substitutions in an eighteen-residue antimicrobial peptide dramatically reduce toxicity and affect the structure of the peptide in subtle ways.

19. Currently, the identity of the preptin receptor is unknown. Therefore it is not possible to model the preptin-receptor interaction, or to perform cross-linking or mutagenesis experiments to map the preptin binding site. Furthermore, it is not possible to screen for compounds that interact with the preptin receptor using high-throughput *in vitro* assays.

20. Clearly the state of the field is such that even the skilled artisan can not predict or easily test the effect of amino acid substitutions and deletions on the activity of preptin, especially for the new application of treating bone conditions.

(5) the breadth of the claims

21. An enormous number of peptides are encompassed in the scope of the instant application. Claims 1-38 are drawn to preptin, preptin analogues and preptin agonists. The breadth of these claims is significant. The term preptin as defined in the specification encompasses all sequences of formula (I): 512 different peptide sequences. Analogs include functional equivalents of all 512 sequences of Formula (I). Functional equivalents include all proteins which are immunologically cross-reactive with and have substantially the same function as preptin

including fragments, active sites, substitutions, additions, deletions or fusions with other amino acids. A preptin agonist is a compound which has a high affinity for a preptin-binding receptor and promotes the proliferation of bone cells. A preptin agonist can be a peptide between 17 and 110 amino acids in length that contains any part of SEQ ID NOs: 1, 2 or 3. Sequences with at least 60% identity to SEQ ID NOs: 1, 2 and 3 are claimed.

(6) the amount of direction or guidance presented; (7) the presence or absence of working examples

22. Despite the lack of predictability and the breadth of the claims, the specification provides only limited working examples: the effect of rat preptin on the promotion of bone cell proliferation, the induction of phosphorylation of p42/p44 MAP kinases in bone cells, and the promotion of bone growth *in vivo* and the effect of human preptin on the promotion of bone cell growth. The specification does not provide an assay for identifying potentially active compounds from the vast number of claimed species or a means to predict which species would be effective.

(8) the quantity of experimentation necessary

23. The skilled artisan would be burdened with undue experimentation in determining if a preptin analogue or agonist would be effective at treating bone conditions.

24. Considering the factors above, the specification while enabling for the use of rat and human preptin (SEQ ID NOs:2 and 3, respectively), is not enabling for the use of all other preptin analogues or agonists in the claimed methods and applications.

25. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

26. Claims 1, 3-13, 15-25 and 27-38 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. These claims are drawn to preptin agonists which are defined in the specification as those compounds exhibiting a tight binding affinity to the preptin receptor. The identity of the preptin receptor is not known. Thus, it is not possible to measure the affinity of a potential agonist to determine if it meets the definition of agonist outlined in the specification. The term "preptin agonist" is therefore indefinite.

Claim Rejections - 35 USC § 103

27. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

28. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any

evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

29. Claims 37 and 38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cooper *et al.* (WO 00/78805, reference AL in the Information Disclosure Statement of 02/01/2005). Cooper *et al.* teach preptin but do not teach instructions for its use in treating bone disease. It has been held that combining printed instructions and an old product into a kit will not render the claimed invention nonobvious even if the instructions detail a new use for the product, In re Ngai, 367 F.3d 1336, 1339, 70 USPQ2d 1862, 1864 (Fed. Cir. 2004). See MPEP 2106. Since the prior art meets the product claimed, the limitations of the claim have been met and a *prima facie* case of obviousness has been established

Conclusion

30. No claims are allowed.

31. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christina Bradley whose telephone number is (571) 272-9044. The examiner can normally be reached on Monday through Friday, 8:30 A.M. to 5:00 P.M.

32. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang can be reached on (571) 272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

33. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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6/20/12
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